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Brief Clinical Report

Severe Hajdu-Cheney Syndrome With Upper Airway Obstruction

Pamela A. Crifasi,[1] Marc C. Patterson,[2] Denise Bonde,[3] and Virginia V. Michels[1]*

[1]*Department of Medical Genetics, Mayo Clinic, Rochester, Minnesota*

[2]*Department of Child and Adolescent Neurology, Mayo Clinic, Rochester, Minnesota*

[3]*Olmsted Medical Clinic, Rochester, Minnesota*

Hajdu-Cheney syndrome is an autosomal dominant disorder of acroosteolysis, skull deformities, characteristic facial abnormalities, osteoporosis, joint laxity, early loss of teeth, hearing loss, and a hoarse voice. We report on an 8 1/2-year-old boy with Hajdu-Cheney syndrome and cystic kidney disease, congenital heart disease, hydrocephalus, cleft lip and palate, hydrosyringomyelia, club feet, splenomegaly, hypospadias, vertebral anomalies, and upper airway obstruction. A review of 44 patients did not uncover any other patients with all of these manifestations, nor any patient with upper airway obstruction. Hajdu-Cheney syndrome appears to encompass a broader phenotype than previously recognized. The documentation of these additional anomalies is valuable because the findings of acroosteolysis and osteoporosis can present later in the course. Am. J. Med. Genet. 70: 261–266, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Hajdu-Cheney syndrome; acroosteolysis; cystic kidneys; upper airway obstruction; multiple congenital anomalies

INTRODUCTION

Hajdu-Cheney syndrome comprises acroosteolysis, skull deformities, typical facial anomalies, and osteoporosis. Familial cases are compatible with autosomal dominant inheritance and many sporadic cases have been reported. This syndrome was first described by Hajdu and Kauntze in 1948 and subsequently by Cheney [1965]. Since that time at least 42 other patients have been described. Several had additional manifestations including cystic kidneys [Rosenmann et al., 1977; Zahran et al., 1984; Van Den Houten et al., 1985; Kaplan et al., 1995], congenital heart disease [Adès et al., 1993; Blery et al., 1984; Zahran et al., 1984; Van Den Houten et al., 1985; Kaplan et al., 1995; Kaler et al., 1990], hydrocephalus [Rosenmann et al., 1977; Zahran et al., 1984; Van Den Houten et al., 1985; Kaplan et al., 1990; Adès et al., 1993; Pellegrini and Widdowson, 1991], cleft palate [Rosenmann et al., 1977; Kaplan et al., 1995], and hepatosplenomegaly [Herrmann et al., 1973; Rosenmann et al., 1977; Adès et al., 1993]. We describe a patient with classic Hajdu-Cheney syndrome and all of these less common manifestations. This Hajdu-Cheney patient appears to be one of the most severely affected patients reported to date. A review of the literature follows.

CLINICAL REPORT

The patient was born at term after an uneventful pregnancy. Birth weight was 3.9 kg. At birth, he was noted to have a right cleft lip and palate, club feet, abnormal positioning of hands, patent ductus arteriosus, ventricular septal defect, and decreased muscle tone. His PDA was ligated. He had poor weight gain, with spitting up and loose stools. At 6 weeks he began having "stiffening spells." EEG and MRI findings were normal. Hypocalcemia was noted. Enlarged kidneys were detected by palpation and ultrasound study at 6 weeks showed large, glomerulocystic kidneys with reflux. His development was delayed; he sat at 1 year and walked alone at 21 months. A conductive hearing loss was found at 2 1/2 years. Ophthalmologic findings and peripheral blood chromosomes were normal.

The patient was referred at 2 9/12 years for evaluation of developmental delay. His weight was then 12.5 kg (15th centile) and length was 91.0 cm (25th centile). His head circumference was 51.7 cm (75–90th centile).

*Correspondence to: Dr. Virginia V. Michels, Department of Medical Genetics, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

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The fontanels were not palpable. The forehead appeared large and square. He had mild blepharophimosis, full cheeks, a slightly prominent jaw, and apparently low-set ears. His cleft lip and palate had been repaired. He had a short neck with limited rotation, excessively lax joints, broad, stubby fingers, broad fleshy feet, and first degree hypospadias. Serum calcium and parathyroid hormone levels were normal. Radiographs of the hands were normal with appropriate bone age. No specific diagnosis was made at that time.

When he was reevaluated at 5 years, frequent upper respiratory tract infections and anosmia were reported. He had normal cognitive development. He was wearing hearing aids for a conductive loss. Synophrys, thick eyelashes, upswept anterior hair line, prominent and long philtrum, and splenomegaly were present. Roentgenograms of the spine showed multiple congenital vertebral malformations and failure of segmentation of the cervical spine.

At 6 1/2 years, his head size had disproportionately increased to 55.5 cm (>90th centile). Dolichocephaly, thick coarse hair, short neck, "gravely" voice, and joint laxity were noted. His breathing appeared slightly obstructed, possibly due to upper airway obstruction. His mother noted that his face had become fuller and his anterior chest more prominent. Additional investigations, including repeat urine metabolic screen (including urine for oligosaccharides), skin biopsy for cytogenetic studies, and electron microscopy studies for lysosomal storage disease, were performed. Results of all these investigations were normal. White blood cell α-mannosidase and α-mannosidase in cultured fibroblasts measured 0.83 U/10^{10} cells (normal 1.5–3.33) and 0.34 U/g protein (normal 0.71–5.90), respectively. White blood cell α-mannosidase activity was normal in both parents. The significance of the decrease mannosidase levels is unclear, but the levels are higher than generally reported in classic deficiency.

MRI findings of the head at 6 8/12 years demonstrated platybasia with basilar invagination. Herniation of the cerebellar tonsils through the foramen magnum with associated obstructive hydrocephalus was visualized. MRI of the spine showed two areas of hydrosyringomyelia, one from C5 to T2, which measured 1.2 cm in width at C7, and the second from T8 to T11. He later received a ventriculoperitoneal shunt, which required several revisions. Evaluation at age 7 4/12 years showed venous prominence over his forehead, unusual facial appearance, and hyperextension of his extremely short neck (Fig. 1). Psychometric testing gave an IQ of 120. X-ray examination of hands showed acroosteolysis of the distal phalanges and a delay in skeletal maturation of between 1 and 2 standard deviations. The diagnosis of Hajdu-Cheney syndrome was made at that time. Lumbar spine radioactive bone mineral analysis resulted in a value 0.51 g/cm^2 (less than the fracture threshold of 0.85). He be-

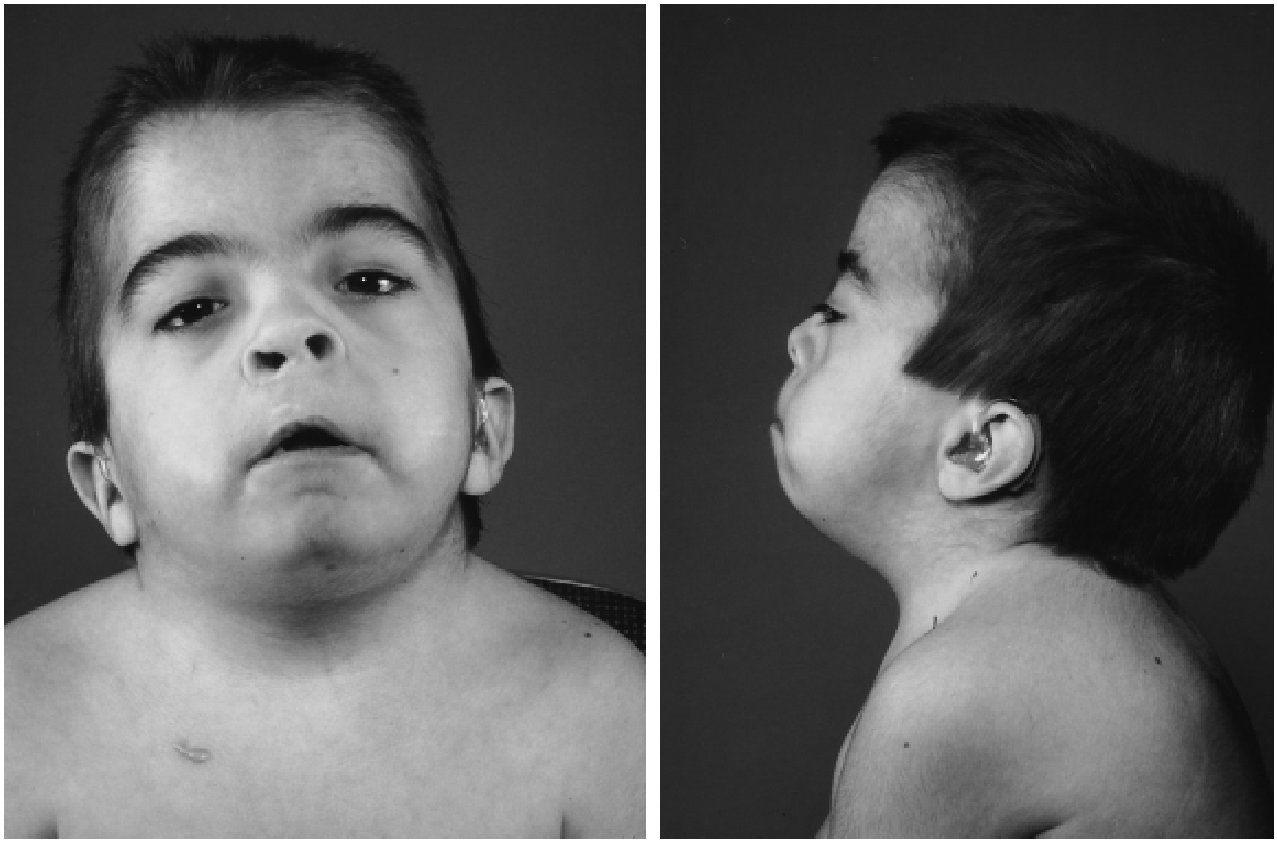

Fig. 1. Note synophrys, cleft lip repair, long philtrum, low set, posteriorly angulated ears with hearing aids in place, short thick neck, and hyperextension of neck.

gan treatment for osteoporosis with increased calcium intake through multivitamins and milk.

After his mother noted that he had an interrupted breathing pattern while asleep, a sleep study was performed that showed 18 disordered breathing events per hour. Most were obstructive hypopneas or apneas, some of which had a possible central component. The oxyhemoglobin was noted to drop to 72%. He was treated with nighttime oxygen by nasal canula. Nasoseptal surgery was done at another institution with no improvement in the nighttime breathing. He had no sign of pulmonary hypertension by electrocardiogram or echocardiogram. His VSD had decreased in size spontaneously.

At age 8 3/12 years his face appeared fuller, his adult teeth were loose, his neck circumference was increased, veins were visible over the anterior abdomen and chest, and his abdominal girth had enlarged (Fig. 2). Results of liver function tests were normal. Abdominal ultrasound study showed splenomegaly but normal liver texture and Doppler flow through the portal vein. The reasons for the venous pattern and increased neck and abdominal size was unclear. In the last year, upper airway obstruction has become a significant management problem. MRI of the neck showed prominent tissue in the lower neck deep to the sternocleidomastoid muscles near the great vessels thought to represent prominent venous confluence, with a high aortic arch as shown by echocardiogram.

Family history is unremarkable; both parents are normal and not consanguineous, two unaffected sisters were born after the propositus.

DISCUSSION

The original patient of Hajdu and Kauntze was a 37-year-old accountant who presented with headache, blurred vision, deafness, history of increasing head size, short stature, teeth extracted because of decay, high palate, short neck, and short, fleshy fingers. Radiographs showed extreme basilar impression, separated sutures, wormian bones, absent frontal sinuses,

Fig. 2. Note short stature, abnormal posture, surgical scars, and malformed feet.

TABLE I. Major Birth Defects in Hajdu-Cheney Syndrome*

Reference	Hydrocephalus	Heart defect	Renal cysts	Cleft palate
Adès [1993]	+	+	–	–
Blery [1984]	–	+	–	–
Chodoroff [1984]	+	–	–	–
Kaler [1990]	–	+	–	–
Kaplan [1995]	+	+	+	+
	–	–	+	–
Pellegrini [1991]	+	–	–	–
Rosenmann [1977]	+	–	+	+
Van den Houten [1985]	–	+	+	–
Williams [1977]	+	–	–	–
Zahran [1984]	–	+	+	–
Our patient	+	+	+	+[a]

*Hajdu-Cheney literature reports were reviewed for the presence of significant associated complications. Zugibe and Silverman described findings in the same patient over time.
[a]Cleft lip and palate.

osteoporosis, and acroosteolysis [Hajdu and Kauntze, 1948]. Cheney described a family in which the mother had severe, intermittent back pain, short stature, short neck, high palate, early loss of teeth, acroosteolysis, kyphosis, broad stubby fingers, prominent occiput, and basilar impression. These findings have become the hallmark of the Hajdu-Cheney syndrome (HCS). Evaluation of three of her adult children showed similar findings. Her 13-year-old daughter was asymptomatic but had basilar impression [Cheney, 1965].

Reports of at least 40 other patients with this syndrome since that time were found in the radiological, pediatric, endocrine, oral surgery, and genetic literature [Greenberg and Street, 1957; Papavasiliou et al., 1960; Chawla, 1964; Dorst and McKusick, 1969; Herrmann et al., 1973; Matisonn and Ziady, 1973; Zugibe et al., 1974; Silverman et al., 1974; Weleber and Beals, 1976; Brown et al., 1976; Giula et al., 1976; Rosenmann et al., 1977; Williams, 1977; Elias et al., 1978; Vanek, 1978; Wendel and Kemperdick, 1979 Iwaya et al., 1979; Kawamura et al., 1981; Zahran et al., 1984; Chodoroff et al., 1984; Blery et al., 1984; Niijima et al., 1984; Van Den Houten et al., 1985; Udell et al., 1986; Jacobson and Edekien, 1986; Kaler et al., 1990; Nunziata et al., 1990; Herscovici et al., 1990; Diren et al., 1990; Pellegrini and Widdowson, 1991; Kawamura et al., 1991; Adès et al., 1993; Zeman et al., 1994; O'Reilly and Shaw, 1994; Muller et al., 1994; Kaplan et al., 1995; Nishimura et al., 1996]. It became apparent that other signs were commonly found in HCS including a characteristic face described as broad with apparently low-set ears, hypertelorism, bushy eyebrows, long philtrum, broad nose, thick or coarse hair, and micrognathia (Hajdu's patient had prognathism). Also there are patients with Hajdu-Cheney phenotype who have major congenital birth defects or develop additional serious complications. Rosenmann described a 15-year-old boy with rapidly progressive glomerulonephritis and hypertension, polycystic kidneys, and HCS [Rosenmann, 1977]. He died 2 weeks after presentation of heart failure. Zahran presented a HCS patient with renal cysts and hypospadias who developed hypertension [Zahran et al., 1984]. An infant born to a mother with HCS had similar anomalies and cystic kidneys [Van Den Houten et al., 1985]. Finally, Kaplan et al. [1995] reported on two unrelated patients with HCS and polycystic kidneys. None of these five patients had a family history of polycystic kidney disease.

Congenital heart disease was reported previously in six patients. Patent ductus arteriosus was documented three times [Zahran et al., 1984; Blery et al., 1984; Kaplan et al., 1995], isolated VSD once [Van Den Houten et al., 1985], aortic regurgitation, aortic stenosis, and mitral regurgitation once [Kaler et al., 1990], and PDA and VSD once [Adès et al., 1993]. Hydrocephalus was reported in six HCS patients [Rosenmann et al., 1977; Kaplan et al., 1995, Adès et al., 1993; Pellegrini and Widdowson, 1991; Chodoroff et al., 1984; Williams, 1977] and cleft palate twice [Rosenmann et al., 1977; Kaplan et al., 1995].

Interestingly, the findings of hydrocephalus, congenital heart defects, renal cysts, and cleft palate have occurred together in a few patients (Table I). This patient is the second to have four of these complications. The other was the infant born to a Hajdu-Cheney mother. That patient died at age 2 days on a ventilator.

A summary of the phenotypic features of the 44 patients previously reported is given in Table II. However, all of the possible manifestations of HCS were not addressed in every patient. It is clear that HCS patients have a wide variety of findings. Hajdu and Cheney's original patients presented as adults and indeed the major findings, such as acroosteolysis, are often not evident in childhood. Patients may present in adulthood with back or finger pain, with finger changes ("shrinking fingers"), or with headaches. However, there are some individuals with more severe manifestations who come to attention early in life.

This patient has had ongoing medical problems, which have required repeated procedures. During his first year, evaluation and/or treatment was required for a club foot deformity, failure to thrive, congenital heart disease, urinary reflux and cystic kidneys, and cleft lip and palate. Subsequently he has been evaluated and treated for hearing loss, obstructive hydrocephalus, upper airway obstruction, cervical malformations, splenomegaly, ongoing foot problems, acroosteolysis, and progressive skeletal deformities. It is important to note that Hajdu's patient and the patient reported here both had increasing head size beyond infancy which provided an important clue to the underlying hydrocephalus. It is important to continue to

TABLE II. Manifestations in 44 Patients With Hajdu-Cheney Syndrome*

Finding	Number	Our patient
Acroosteolysis	39[a]	+
Broad stubby fingers	28	+
Short stature	25	+
Basilar invagination	24	+
Wide sutures	24	
Teeth-early loss/loose	24	+
Basilar invagination	24	+
Joint laxity	23	+
Dolichocephaly	21	+
High palate	17	
Prominent eyebrows	17	+
Hearing loss	16	+
Kyphosis/scoliosis	16	
Positive family history	14	
Osteoporosis	14	+
Sella elongation	13	
Low set ears	12	+
Fractures	12	
Absent frontal sinus (adult)	11	
Cervical spine abnormalities	11	+
Short neck	9	+
Micrognathia	9	
Mandibular hypoplasia	8	
Hypertelorism	8	
Thick/coarse hair	8	+
Motor delay	7	+
Normal karyotype	7/7	+
Long philtrum	7	+
Headaches	6	
Umbilical/inguinal hernia	6	
Congenital heart disease	6	+
PDA 3		
VSD 1		
PDA/VSD 1		+
AR/AS/MR 1		
Cystic kidneys	5	+
Normal IQ	5	+
Uvula abnormalities	5	
Visual changes	5	
Cataracts	1	
Joint dislocation	4	
Bowel malrotation	4	
Mild mental retardation	4	
Hepatosplenomegaly	3	+
Hypertension	3	
Club feet	3	+
Malocclusion	3	+
Cleft palate	2	+ (CL/CP)
Hypospadias	2	+
Cryptorchidism	2	
Upper airway obstruction	–	+

*The findings in reported Hajdu-Cheney patients are tabulated. The patient reported here has the major findings in addition to the less common serious complications.
[a]Five cases without reported acroosteolysis were children.

measure head size in older patients, beyond the age for which such measurements usually are obtained. The cause of his upper airway obstruction is unclear. Some of the abnormalities resemble those seen in the mucopolysaccharidoses. With the exception of the infant who died at 2 days, this patient appears to have had the most complicated course with abnormalities in every organ system that was reported previously in variable combinations. Reports of other patients with severe upper airway obstruction were not found.

Fourteen of the 44 patients reviewed had an autosomal dominant inheritance pattern while the remaining cases were apparently sporadic. There were no differences in phenotype between the sporadic and inherited forms. The sporadic cases may represent new mutations with decreased reproductive fitness. No chromosome defect has been found. Neither the gene for Hajdu-Cheny syndrome nor a primary metabolic defect has been identified.

Management issues for patients with Hajdu-Cheney syndrome potentially pertain to all major organ systems. Patients typically have skull and spine malformations putting them at risk for hydrocephalus, cervical instability, severe basilar impression, scoliosis, and kyphosis. Several patients have presented with headaches due to hydrocephalus. Clefting and micrognathia can make feeding difficult in the newborn period. These patients should be evaluated for congenital heart disease. They are at risk for recurrent upper respiratory infections and pneumonia. There is a risk for upper airway obstruction and sleep apnea as demonstrated by this patient. Evaluation of the kidneys should be considered even in the absence of symptoms in early childhood as they are a risk for dysplastic/cystic kidneys with sequelae. Other complications include multiple dislocations and fractures. One child was initially evaluated for child abuse because of a fracture. Treatment for osteoporosis should be considered. The associated anomalies can be difficult for some patients and may require counseling and plastic surgery. While most patients have a normal IQ, some have mild mental retardation. Back or hand/foot pain may develop. Management of these ongoing problems can be difficult.

Because the classic finding of acroosteolysis is not present in early childhood, this diagnosis should be kept in mind in patients who initially present with other manifestations.

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